REMARKS

The Office Action set forth the following rejections:

Claims 1-5 were rejected under 35 U.S.C. § 101 and § 112, first paragraph, as lacking utility; and

claims 4 and 5 were rejected under 35 U.S.C. § 112, first paragraph, as not being enabled.

No claim amendments are currently made.

§ 101 and § 112 utility rejections of claims 1-5

The Section § 101 utility requirement has a relatively low threshold. All that

Applicants need to demonstrate is that the claimed invention has a well-established utility for some purpose, either explicitly or implicitly. The utility must be specific, substantial and credible. According to the MPEP, the "specific and substantial" requirement excludes "throw-away", "insubstantial" or "nonspecific" utilities (*See*, MPEP § 2107(II)(B)(1)(i)). Moreover, an applicant needs to provide only one credible assertion of specific and substantial utility for each claimed invention to satisfy the utility requirement (*See*, MPEP §2107(II)(B)(1)(ii)).

Credibility

According to the MPEP, in most cases, an applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. §101. Moreover, the asserted utility must be regarded as credible unless (A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion. (*See*, MPEP §2107.02(III)(B)).

Applicants respectfully suggest that the asserted utilities of this invention (for example, the use of the claimed polypeptide as bait for identifying calpain inhibitors selective for CAPN11, and subsequent use of the inhibitors in treatment of disorders associated with CAPN11 activity) are credible.

Specific and Substantial Utility

Applicants respectfully maintain that the utilities of the claimed invention are specific and substantial. The polypeptides claimed in the invention may be useful, for example, as a bait for identifying substances, which are able to inhibit enzymatic activity of the polypeptide (*See*, specification, page 4, lines 1-21).

A "specific" utility is specific to the subject matter claimed. The MPEP makes clear that the PTO should distinguish between situations where a specific use is disclosed and situations where it is not identified why the invention is considered useful. (*See*, MPEP §2107.01(I)(A)). While a general statement of diagnostic utility without disclosure of what condition can be diagnosed is insufficient to demonstrate specific utility, the specific utility is present where an applicant discloses a specific biological activity and reasonably correlates the activity to a disease condition.

A "substantial" utility defines a "real world" use. The MPEP states that "any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "substantial" utility." (*See*, MPEP §2107.01(I)(B)).

Applicants respectfully submit that the invention has specific and substantial utility. Applicants demonstrated that CAPN11 is most strongly expressed in testis. Also, Applicants determined the chromosome on which the human CAPN11 gene is located. Because it is known that calpains in other

tissues are involved in certain processes, such as germ cell apoptosis and regulation of tissue-specific transcription factors, it is reasonable to suggest that CAPN11 may be involved in similar processes in testis. Moreover, the specification discloses that the claimed polypeptide may be used as a bait for identifying substances, which are able to inhibit enzymatic activity of the polypeptide. In turn, these inhibitors may be used for treatment of disorders associated with or linked to a non-physiologically elevated CAPN11 activity such as infertility in men. (*See*, specification, page 4, lines 1-26).

These utilities are specific and substantial. It is not as if Applicants are claiming that polynucleotides or polypeptides might be useful in treating unspecified disorders, or that the protein has unspecified useful properties. In contrast, the application discloses a relation to specific processes, such as germ cell apoptosis. A person skilled in the art knows that cysteine proteases are involved in apoptosis (*See*, for example, *Billing, H., Chun, S.-Y., Eisenhauer, K. and Hsueh A. J. W., Human Reprod. Update, Vol. 2, No. 2, pp. 103-107 (1996)).* It has been shown that proteases play a great role in apoptosis. (*See*, for example, *Martin, S. J. and Green, D. R., Cell, Vol. 82, pp. 349-352 (1995))*. The use of the invention to advance treatment of the specified disease (for example, male infertility) is providing a public benefit. Moreover, Applicants respectfully maintain that the use of inhibitors of CAPN11 activity to treat infertility inherently demonstrates utility for the protein CAPN11 itself.

Accordingly, the present application identifies a specific and substantial utility for the invention and discloses enough information about the invention to make its usefulness immediately apparent to those familiar with the technological field of the invention.

Response to the Office Action's Arguments

Applicants will refer to the (A) to (D) nomenclature of the Office Action.

(A) Applicants respectfully disagree with the Office Action's position that RNA encoding the protein of SEQ ID NO:2 is not specific for testis. Northern blot demonstrates a very strong band in the testis lane (Fig. 3D). Even if much weaker signals were detected in the thymus and the mammary gland, the significance of this is unclear because further investigation of thymus RNA by Northern blot analysis produced no signal, despite long exposure times. This weak signal is probably attributable to cross-hybridization with related mRNAs (*See*, specification, page 2, line 45 to page 3, line 4). As the specification states, testis is the main expression site of CAPN11.

Applicants respectfully maintain that it is reasonable to suggest that CAPN11 is involved in processes such as germ cell apoptosis or regulation or testis-specific transcription factors. Contrary to the Office Action's position, Applicants do not merely guess what processes CAPN11 might be involved in; rather Applicants present a convincing and reasonable theory. CAPN11 is expressed most strongly in testis; its specific DNA sequence is identified; it is known that calpains are related proteins; it is demonstrated that the novel CAPN11 protein has the properties typical of other calpains; therefore, it is reasonable to suggest that CAPN11 would be involved in processes in which calpains in other tissues are involved.

(B) Moreover, Ben-Aharon et al provide further support for this theory. The article states that expression of CAPN11 during spermatogenesis and its localization in spermatozoa suggest that it is involved in regulating calcium-dependent signal transduction events during meiosis and sperm functional processes. It is irrelevant for what purpose the Office Action cited this reference.

For whatever purpose it was cited, it convincingly demonstrates that it is more likely than not that the asserted utility is true. In the words of the reference, "these studies suggest that CAPN11 has the appropriate temporal and spatial distribution to be involved in regulating key signal transduction events and processes of cytoskeletal remodeling during meiosis, spermiogenesis and sperm function." (*See*, Ben-Aharon, at 772, right column).

While it is true that the specific substrate for CAPN11 has not yet been identified, the reference states that "a number of known calpain substrates are present in spermatogenic cells that are potential CAPN11 targets." Just because the substrates and functions of CAPN11 are not yet fully identified, does not negate the utility for the claimed invention. A skilled artisan would therefore know the specific and substantial utility of CAPN11.

Applicants are not required to identify with 100% certainty the processes at which CAPN11 is involved, as the Office Action seems to suggest. This is not the standard. As the MPEP states, an applicant is not required to provide evidence such that it establishes an asserted utility as a matter of statistical certainty. (*See*, MPEP §2107.03.(VII)). Instead, Applicants need to demonstrate that the asserted utility is more likely than not true.

Where, as here, on the basis of Applicants' work and on the basis of what is known in the art, it is reasonable to identify processes and diseases which may likely involve the claimed sequence, the requirement of specific and substantial utility is met. Respectfully, the Examiner did not demonstrate that it is more likely than not that a person of ordinary skill in the art would not consider the asserted utility specific and substantial.

(C) Applicants respectfully disagree that the protein of SEQ ID NO:2 cannot be used for identifying inhibitors because an assay for measuring activity has not

been provided. It is well known for a person skilled in the art that enzyme activity can be determined by time dependent measurements of substrate and product concentrations. Values such as extinction, potential, and conductivity are routinely measured. Photometrical methods, for example, are based on the use of dilution series and concentration measurements at a suitable wavelength, for example, at 240 nm. These methods are well known and can be applied to the claimed subject-matter without undue experimentation.

Applicants claim a single sequence –SEQ ID NO:2. Accordingly, only a certain number of potential inhibitors inhibit the polypeptide expressed by this sequence. The inhibitors are suitable for the treatment of disorders associated with a non-physiologically elevated CAPN11 activity (*See*, specification, page 4, lines 23-26). The treatment of infertility in men is a substantial and credible utility. To find these inhibitors, one needs to know their counterpart (the related protein). Thus, a utility of the inhibitor implicitly also proves the utility of CAPN11.

D) As Applicants explained, Ben-Aharon et al. state that their findings indicate that CAPN11 fits into the category of spermatogenic cell-specific proteins (*See*, Ben-Aharon, page 770, Discussion). Also, other publications show that intracellular cysteine proteases, to which CAPN11 likely belongs, are related to male fertility. (*See*, for example, *Honbou, K. et al., JBC Papers in Press, published on June 8, 2003 as Manuscript M305878200.*)

In conclusion, it is at least highly likely that CAPN11 is related to fertility in men and is thus useful in treating and/or diagnosing related diseases. Accordingly, the claimed invention has a specific and substantial credible utility.

§ 112, written description rejections of claims 4 and 5

The Office Action rejected claims 4 and 5 as containing subject matter which was not described in the specification in a way as to reasonably convey to a skilled worker that the inventors at the time of the application was filed had possession of the claimed invention.

Applicants respectfully disagree. The Examiner's attention is again directed to page 4 of the application where a CAPN11 selective compound is defined as a compound that selectively blocks the activity of CAPN11 at least 10-fold, preferably 25-fold more than it blocks the activity of other calpains. This would clearly lead one of skill in the art to conclude that a method for identifying an inhibitor of the particular protein is taught. As already mentioned above, it is well known for a person skilled in the art that the enzyme activity can be determined by time dependent measurement of substrate and product concentrations. On page 4, the specification clearly teaches that the enzyme activity of CAPN11 is a Ca-dependent protease activity. This would clearly lead one of skill in the art to conclude that a method for identifying an inhibitor of this particular protein is taught.

Thus, a skilled worker would have clearly concluded that Applicants had possession of the invention as defined in claims 4 and 5. Accordingly, this rejection should be withdrawn.

Favorable consideration of claims 1-5 as presently amended is respectfully requested.

Respectfully submitted,

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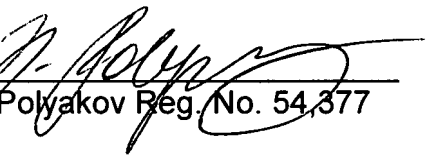

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